Abstracts

TIME-OF-DAY OF PEMBROLIZUMAB INFUSION AND CLINICAL OUTCOMES OF PATIENTS WITH NSCLC: TOO SOON TO PROMOTE MORNING INFUSIONS

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Background Circadian oscillations in T-cell function may influence outcome from cancer immunotherapy.1 Evidence for an association between time-of-day of immune checkpoint inhibitors (ICI) infusion on outcomes in patients with non-small cell lung cancer (NSCLC) is scanty.

Methods In this multicenter study, we retrospectively evaluated the association between time-of-day patterns of pembrolizumab infusion and outcomes in a cohort of patients with treatment-naive metastatic NSCLC with PD-L1 expression ≥50% treated from June 2016 to September 2021. Receipt of ≥20% vs <20% of infusions after the 16.30h cut off time (“late infusions”) was set as threshold for analysis. In addition, we explored increasing thresholds for late infusions based on centre-specific distribution of cut-off times.

Results Overall 180/262 patients received ≥4 cycles and were eligible, 136 (75.5%) and 44 (24.5%) patients respectively received <20% and ≥20% of evening infusions. Evening infusions were associated with a lower number of cycles (median: 14 vs 8, p = 0.0002). Following a propensity score matching (PSM) accounting for age, PD-L1 expression, ECOG-PS, bone metastases, smoking status and sex, 78 and 44 patients were matched from the <20% and the ≥20% evening infusions cohorts. Median OS and PFS of patients who received ≥20% and <20% of evening infusions were 27.8 vs 47.1 months (p = 0.11) (figure 1A), and 6.6 vs 19.7 months (p = 0.056) (figure 1B), respectively. Evening infusions did not affect the risk of death (HR 1.53, 95%CI: 0.88-2.76) or disease progression/death (HR 1.51, 95%CI: 0.95-2.42) at the multivariable analysis. When including the number of cycles in the PMS, patients who received <20% and ≥20% of evening infusions experienced similar OS and PFS estimates (figure 1C,D). The exploratory analyses of OS according to increasing quartiles with the 16.30h threshold and the centre-specific median time-of-day threshold across the entire population and the landmark population highlighted that both the receipt of 0% and 100% of evening and late infusions were associated with an increased risk of death (table 1), while after adjusting for the number of administered cycles, no proportion of late infusions was significantly associated to the risk of death.

Figure 2 provides a representation of the distribution of cycles across progressive thresholds for proportions of evening (16.30h threshold) and late (median time-of-day threshold) infusions according to incremental quartiles, highlighting duration of therapy as an inherent bias in retrospective analyses.

Conclusions Translational dynamic studies of peripheral T-cell immunity are warranted while prospective trials should be conducted before promoting morning infusion in clinic.

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REFERENCE

Abstract 512 Figure 1 Kaplan-Meier survival estimates among the matched landmark population (=4 cycle) according to the receipt of ≥20% or <20% of evening infusions. Matching variables were: age, PD-L1 TPS, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), bone metastases, smoking status and biological sex. (A) Overall survival (OS); (B) Progression Free Survival (PFS). Kaplan-Meier survival estimates among the matched landmark population (=4 cycle) according to the receipt of ≥20% or < 20% of evening infusions, including the number of administered cycles in the matching procedure. (C) Overall survival (OS); (D) Progression Free Survival (PFS)
Abstract 512 Figure 2  Graphical representation of the distribution of median number of administered cycles across progressive thresholds for proportions of late infusions according to incremental quartiles. No infusions after 16.30h YES: 5 (IQR: 2-11.2), No infusion after 16.30h NO: 10 (IQR: 4-22); >25% infusions after 16.30h: 4 (IQR: 2-6.7), <25% infusions after 16.30h: 8 (IQR: 3-18.7); >50% infusions after 16.30h: 3.5 (IQR: 2.5-5.5), <50% infusions after 16.30h: 7 (IQR: 3-18); >75% infusions after 16.30h: 1 (IQR: 1-4), <75% infusions after 16.30h: 7 (IQR: 3-17.2); All infusions after 16.30h YES: 1 (IQR: 1-2), All infusions after 16.30h NO: 7 (IQR: 3-17). No infusions after median ToD YES: 2 (IQR: 1-5), No infusions after 16.30h NO: 8 (IQR: 3-18); >25% infusions after median ToD: 7 (IQR: 3-17), <25% infusions after 16.30h: 6 (IQR: 2-15.5); >50% infusions after median ToD: 5 (IQR: 2-11), <50% infusions after 16.30h: 11 (IQR: 3.2-20.7); >75% infusions after median ToD: 4 (IQR: 2-7.5), <75% infusions after 16.30h: 10 (IQR: 4-21); All infusions after median ToD YES: 2 (IQR: 1-5.5), All infusions after 16.30h: 9 (IQR: 4-20). IQR: inter-quartile range; ToD: time-of-day.

Abstract 512 Table 1  Univariable and multivariable analysis of the risk of death according to incremental quartiles of evening infusions for each patients using the 16.30h threshold and centre-specific cut-offs (median time-of-day at each centre) among the whole study population and the landmark population. Increasing quartile of late infusions was first tested alone and then adjusted for the number of administered cycles. HR: hazard ratio; CI: confidence intervals.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Overall population HR (95% CI) for risk of death</th>
<th>Landmark population HR (95% CI) for risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infusions after 16.30h</td>
<td>1.00 (0.22-4.94)</td>
<td>1.00 (0.41-2.72)</td>
</tr>
<tr>
<td>&lt;25% of infusions after 16.30h</td>
<td>1.00 (0.84-1.19)</td>
<td>1.00 (0.84-1.19)</td>
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<tr>
<td>≥25% of infusions after 16.30h</td>
<td>1.00 (0.84-1.19)</td>
<td>1.00 (0.84-1.19)</td>
</tr>
<tr>
<td>No infusions after median ToD</td>
<td>1.00 (0.31-2.99)</td>
<td>1.00 (0.31-2.99)</td>
</tr>
<tr>
<td>&lt;25% of infusions after median ToD</td>
<td>1.00 (0.31-2.99)</td>
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<td>≥25% of infusions after median ToD</td>
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